amount does not induce a pathological response in the mammal when administered parenterally, said composition being in a form adapted for oromucosal contact.

REMARKS

Claims 1-5, 7-13 and 15-22 presently appear in this case. No claims have been allowed. The official action of October 21, 1999, and the references relied upon therein have now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to methods for stimulating systemic host defense mechanisms in a mammal or for treating a systemic autoimmune mycobacterial neurodegenerative, parasitic or viral condition in a mammal by administering a therapeutically effective amount of an interferon via oromucosal contact. The amount is from about 21.4 IU/kg/day to about 2.9×10^4 IU/kg/day or a total of about 1,500 to about 20×10^6 IU/day.

Claims 13 and 14 have been objected to as being duplicative.

Claim 14 has now been deleted thus obviating this objection.

Claim 2 has been rejected under 35 U.S.C. §102(b) as anticipated by Cummins for reasons previously discussed. The examiner states that Cummins exemplifies protocols which

involve the cumulative administration of about 4,200 IU of IFN. This rejection is respectfully traversed.

Claim 2 has now been amended to specify that the dosages specified are daily dosages. In this regard, reference is made to page 3 of the specification, lines 22-27, which clarify that the dosages are "per day". In the examiner's analysis of the protocol of Cummins appearing in the official action of September 28, 1998, the examiner states that Cummins discloses administering interferon in solution at 0.7 IU/lb. Thus, for a patient weighing 140 pounds, each dose would consist of 100 IU of interferon. The examiner then states that the interferon was administered twice daily for periods up to 21 days, and that in such protocols then a total of about 4,200 IU of interferon was administered. However, this amount is over a period of 21 days. As acknowledged by the examiner, the maximum daily amount would be 200 IU of interferon for a patient weighing 140 pounds. This dosage is administered by twice daily doses of 100 IU. Such an amount certainly does not anticipate claim 2 which requires a minimum of 1,500 IU/day. Accordingly, reconsideration and withdrawal of this rejection are respectfully urged.

Claims 1-5, 7, 8, 10-12 and 15-18 have been rejected under 35 U.S.C. §102(b) as anticipated by Samo. The examiner states that "oromucosal" administration as employed in the

present disclosure reasonably appears to comprehend conventional intranasal administration. The examiner states that Samo describes the administration of 0.7 - $24x10^6$ IU/day of recombinant hIFN-αA to humans by intranasal (solution spray) administration, divided into two doses per day, and teaches that such doses are effective to prevent, attenuate, or treat viral infection. This rejection is respectfully traversed.

The nasal spray of Samo releases interferon in such a small droplet size that it goes directly to the lungs and does not make contact with the oropharyngeal cavity. The examiner's attention is invited to page 11, lines 12-17, of the present specification where it states:

> For the purpose of the animal experiments described in this specification, it will be clearly understood that the expression "intranasal/oral" or "intranasal plus oral" or "in/or" or "oromucosal" or "oropharyngeal" with reference to the route of administration of IFN is to be taken to mean administration of the IFN preparation deep into the nasal cavity so that it is rapidly distributed into the oropharyngeal cavity, *i.e.* the mouth and throat of the recipient mammal, so as to make contact with the mucosa lining this cavity.

Furthermore, the examiner's attention is invited to page 6, lines 22-30, of the present specification, where it states:

> The IFN may be administered by any means which provides contact of the IFN with the

> oromucosal cavity of the recipient. Thus it will be clearly understood that the invention is not limited to any particular type of formulation. The present specification describes administration of IFN deep into the oromucosal cavity; this may be achieved with liquids, solids, or aerosols, as well as nasal drops or sprays. Thus the invention includes, but is not limited to, liquid, spray, syrup, lozenges, buccal tablets, and nebuliser formulations. A person skilled in the art will recognize that for aerosol or nebuliser formulations the particle size of the preparation may be important, and will be aware of suitable methods by which particle size may be modified.

It is thus clear that the administration must be via the oromucosal cavity, i.e., the mouth and throat of the recipient animal, as opposed to the lungs. Those of ordinary skill in the art understand, as stated in the above-quoted portion of the specification, that when one is using aerosol and nebulizer formulations, the particle size of the preparation is important. Thus, the larger the particle, the more likely that the spray will concentrate in the oromucosal cavity. The smaller the droplets, the more likely that the spray will bypass the oromucosal cavity and be deposited directly in the lungs.

In Samo, the purpose is to treat respiratory infection. The interferon is administered via a metered-dose spray bottle so as to administer the interferon directly to the lungs. This does not meet the limitation of administering

"via oromucosal contact". For clarification, new claim 23 has now been added specifying that the administering step comprises bringing the interferon into contact with the mucosa lining the mouth and/or throat of the mammal being treated, as is supported by the above-quoted portions of the specification. This is clearly not anticipated by Samo whose purpose is to administer the interferon to the lungs, rather than to the mucosa lining the mouth and/or throat.

As to the composition claims, claim 15 has now been amended to specify that the interferon is in a composition with a vehicle or excipient which facilitates contact with the mucosa lining the mouth or throat upon administration, and that the composition is in a form adapted for oromucosal contact. This language no longer reads on the spray bottle of Samo which is a dosage form adapted for administration to the lungs, rather than a dosage form adapted for oromucosal contact. Furthermore, new claim 24 does not read on a nasal spray and cannot be anticipated by Samo. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claims 1-3, 5, 7, 8, 13 and 14, have been rejected under 35 U.S.C. §102(b) as being anticipated by Iida. The examiner states that Iida describes the intranasal administration of doses of 10^1-10^3 units of mIFN-γ to mice and teaches that such administration is effective to prevent,

attenuate or treat infection by Sendai virus. This rejection is respectfully traversed.

Iida suffers the same deficiencies as Samo, discussed above. Iida involves intranasal administration directly to the lungs. In this regard, reference is made to the discussion in the first column of page 232, where it states:

> These results suggest that i.n. [intranasal] administration of these cytokines is likely to cause an inflammatory response, or that it activates the immune system at the administration site (lungs) and consequently stimulates host resistance against the viral infection. [emphasis added]

Thus, Iida explicitly acknowledges that the administration site is the lungs. The present claims require that the administration site be the oromucosal cavity, i.e., the mucosa lining the mouth and/or throat. Accordingly, the size of the particles in the intranasal spray of Iida must have been selected such that the administration site will be the lungs, as opposed to the throat. This does not anticipate any of the present claims for the same reasons discussed above with respect to Samo. Reconsideration and withdrawal of this rejection are, therefore, also respectfully urged.

Claim 9 has been rejected under 35 U.S.C. §103 as being unpatentable over Iida. The examiner states that oromucosal administration as instantly claimed reasonably

appears to comprehend intranasal administration. This rejection is respectfully traversed.

As discussed hereinabove, oromucosal administration does not comprehend intranasal administration by a spray in which the particle size is selected so as to administer the active principle to the lungs, as opposed to the oromucosal cavity. As indicated above, Iida explicitly states that the administration site is the lung. Accordingly, claim 9 is not anticipated or made obvious by Iida. Even if one were to co-administer additional substances in Iida, this would not result in the presently claimed invention. Reconsideration and withdrawal of this rejection are, therefore, respectfully urged.

Claims 1-5 and 7-21 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Cummins '382 in view of either Samo or Iida. The examiner states that the prior art fairly provides motivation to use doses higher than those exemplified by Cummins but lower than those exemplified by Samo and Iida because all of the prior art dosages were known to be effective for the treatment of viral infection. The examiner states that the artisan would reasonably have expected that any intermediate dosage range would likewise be effective. This rejection is respectfully traversed.

The Cummins patent specifies a maximum of about 5 IU/lb per day. This is an extremely low dose and is only disclosed as being useful for administration via the oral and/or pharyngeal mucosa. Thus, one of ordinary skill in the art reading Cummins would not consider it obvious to increase this dosage, notwithstanding the disclosures of Samo and Iida which teach higher doses with other modes of administration. That Cummins considers the low dose maximum to be critical is apparent from more recent publications of Cummins et al. Attached hereto is Cummins et al "Oral Use of Interferon", J. Interferon and Cytokine Res. 19:853-857 (1999). In the second column of page 854, Cummins states:

> One of the paradoxes of the efficiency in the oral use of IFN is the dose effect. Here, "less" is almost always better than "more." In most of the low-dose studies of IFN-α, used orally, where a beneficial dose was identified, increasing the dose did not improve the effect. For example, 50 IU of human IFN-α given orally was more beneficial than 450 IU in treatment of horses with inflammatory airway disease [citation omitted].

Furthermore, one of ordinary skill in the art would understand that there is a difference in the effects of the different modes of administration in view of the fact that Samo discloses that an intranasal dose of 0.7×10^6 daily was ineffective (see Abstract). If Cummmins' maximum dose is effective, and Iida's minimum dose, which is substantially

higher than the maximum dose of Cummins, is ineffective, what would be the motivation to substantially increase the dose in the administration mode of Cummins? The difference in routes of administration is also emphasized by Iida, where intranasal administration worked at dosages where intravenous administration did not.

The present claims are all limited to oromucosal administration. While Cummins discloses oromucosal administration, Iida and Samo do not. Cummins does not teach the dosages of the present claims. These dosages are not made obvious by the disclosures of Samo and Iida, read as a whole, for the reasons discussed above. Reconsideration and withdrawal of this rejection are also, therefore, respectfully urged.

It is submitted that all of the claims now present in the case clearly define over the references of record. Reconsideration and allowance are, therefore, earnestly solicited.

Respectfully submitted,

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